Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
EudraCT Number	2013-001891-39

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

Study dates:	First subject enrolled: 24 September 2013 Last subject last visit: 01 April 2014
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

The study was conducted at 11 sites in 4 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Primary objective	Outcome variables
To investigate the effect of food on the pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours	– Maximum plasma concentration (C_{max}/ $C_{ss,max}$) – Minimum plasma concentration (C_{min}) – Time to reach maximum plasma concentration (t_{max}/$t_{ss,max}$) – Area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}) – Area under the plasma concentration-time curve over the dosing interval τ ($AUC_{0-\tau}$) – Area under the plasma concentration time curve from zero to infinity (AUC) – Apparent plasma clearance following oral administration (CL/F or CL_{ss}/F) – Apparent volume of distribution (V_z/F) – Terminal rate constant (λ_z) – Terminal half-life ($t_{½}$) – Fluctuation index (FI) – Other parameters could be determined as deemed appropriate
Secondary objectives	**Outcome variables**
To investigate the effect of olaparib on the QT interval following oral dosing of the tablet formulation in patients with advanced solid tumours	– Corrected QT interval (QT/RR)
To further investigate the safety and tolerability of olaparib following oral dosing of the capsule formulation in patients with advanced solid tumours	– Adverse events – Physical examination – Vital signs (blood pressure and pulse) – Electrocardiogram parameters – Laboratory parameters (clinical chemistry, haematology and urinalysis)

Study design

This was a 3-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was a randomised, open-label, 2-treatment period crossover study to determine the effect of food on the PK profile of olaparib. Each patient received a single 300 mg oral dose of olaparib (given as two 150 mg tablets) in each of the 2 treatment periods (once in the overnight fasted state and once immediately following a high-fat meal at breakfast time), with a washout period of at least 5 and no more than 14 days between doses. PK and safety assessments for up to 72 hours post-dose, and digital ECG (dECG) up to 24 hours were obtained in each treatment period. Additionally, during the first treatment period, patients underwent baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock-times matched to planned/scheduled assessments on the dosing day (Day 1). Patients checked into the clinic on Day -2 (first treatment period), or on the evening of Day -1 (second treatment period), and remained resident until 24 hours after receiving each dose of olaparib. Patients then returned to the clinic for assessments on Days 3 and 4 of each treatment period. On Day 1 of Part A, patients fasted over the same time period as Day -1. The dECGs performed on Day 1 in each treatment period were clock-matched to the actual times that the Day -1 dECGs were performed in the first treatment period.

Part B of this study was an open-label study with the same patients who participated in Part A. After completion of Part A, following a wash-out period of at least 5 days and no more than 14 days between the last dose in Part A and Day -1 of Part B, and if the patient still met the study entry criteria, they were provided olaparib tablets 300 mg twice daily (bd) for 5 days. Part B determined the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets. As was done for Part A, patients underwent baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock-times matched to planned/scheduled assessments on Day 5 of dosing.

Following completion of Part B, patients could enter Part C and continue to take olaparib tablets (300 mg bd) if they and the Investigator agreed that this was appropriate, providing the baseline safety assessments for Part C were in accordance with the study entry criteria. Patients were required to start Part C immediately after the last dose received in Part B. If toxicity reoccurred following re-challenge with olaparib, and if further dose interruptions were considered inadequate for management of toxicity, then the patient was considered for dose reduction or permanent discontinuation of treatment with olaparib.

Target patient population and sample size

It was planned to recruit approximately 48 patients (male or female) with advanced solid tumours to ensure that at least 42 evaluable patients completed the study.

Based on the estimate of within-patient standard deviation (SD) for log area under the plasma concentration time curve from zero to infinity (AUC) from Studies D0180C00002 and D0180C00003 of 0.26, and assuming a true food effect difference of 5%, 42 evaluable volunteers (21 per-sequence) were required to give 90% power of showing that the 90% confidence interval (CI) for the food effect (ratio of geometric least-squares means of AUC or C_{max} in the fed state to the fasted state) was entirely within the range of 0.8 to 1.25.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Olaparib was supplied as 100 mg and 150 mg tablets for oral administration. Olaparib 100 mg and 150 mg tablets were manufactured by Patheon on behalf of AstraZeneca.

In Part A, patients received 2 single doses of olaparib 300 mg. In Part B, patients received 10 doses of olaparib 300 mg. In Part C, patients took olaparib 300 mg bd.

The batch numbers were 13-001225AZ and 13-002066AZ for 100 mg tablets, and 13-001226AZ and 13-002068AZ for 150 mg tablets.

Duration of treatment

In Part A, patients received a single oral dose of olaparib 300 mg on Day 1 of each of the 2 treatments periods with a washout period of at least 5 and no more than 14 days between doses. In Part B, following a washout period of at least 5 days and no more than 14 days, between the last dose in Part A and Day -1 of Part B, patients received olaparib 300 mg bd for 5 days.

In Part C, patients continued to receive olaparib at a dose of 300 mg bd for a period of 12 months after the date the last patient entered this part of the study. Patients could continue to take olaparib during and after Part C, if they and the Investigator considered it was appropriate, until such time as their disease progressed, the Investigator believed they were no longer deriving clinical benefit, or they stopped taking olaparib for any other reason. Dose interruptions/permanent discontinuation of olaparib was considered if toxicity reoccurred following re-challenge with olaparib, or if dose interruptions were considered inadequate for management of toxicity.

Statistical methods

The objective of the statistical analysis in Part A was to estimate the effect of food on the PK of olaparib, given in the tablet formulation. Following log-transformation, C_{max}, AUC, and AUC_{0-t} of olaparib were separately analysed by mixed-effect analysis of variance (ANOVA), fitting terms for sequence, patient within sequence and treatment (where treatment represented food condition, ie, fed or fasted). Patient within sequence was treated as a random effect in the model. Point estimates and adjusted 90% CIs for the difference between treatments (fed compared with fasted) for C_{max}, AUC, and AUC_{0-t} were constructed. The point estimate and adjusted 90% CIs were then back transformed to provide point and CI estimates for the ratio of interest. No food effect on the PK of olaparib was included if the 2-sided 90% CIs for the ratios of AUC (or AUC_{0-t} as previously noted) and C_{max} were within the range of 0.80 to 1.25.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed compared with fasted) and 90% CIs was also presented.

Pharmacodynamic (ECG) summaries were presented for patients in the QT analysis set by treatment and study day for Part A, and study day for Part B. At each timepoint in

Part B, ECG readings were performed in triplicate for each patient. The mean value of the 3 readings was calculated.

The PD variables (absolute values and change from baseline [pre-dose] on Day 1) were listed and summarised using descriptive statistics. Changes from baseline (time matched day -1) in PD variables were also listed. The QT/QTc outliers were defined as QT/QTc values following dosing that were greater than 450 msec or were increases from baseline (pre-dose) greater than 30 msec. The number and percentage of patients who met the ECG outlier criteria at any assessment after start of olaparib was tabulated by treatment for Part A ("Fed [A]" and "Fasted [A]"), and by study day for Part B ("Day -1 [B]" and "Day 5 [B]").

Safety data were listed and summarised using descriptive statistics.

This study report contains data from Parts A and B of the study only. Data for Part C of this study will be presented in a separate report.

Subject population

A total of 80 patients enrolled, 60 (14 male and 46 female) were randomised into Parts A and B, and received at least one dose of olaparib (20 did not fulfil eligibility criteria). All 60 patients completed Part A of the study. Three patients did not continue into Part B: 1 patient due to death (related to the disease under investigation), 1 patient due to condition under investigation worsened, and 1 patient due to ineligibility to continue into Part B. During Part B 1 patient was discontinued due to condition under investigation worsened, and 55 out of the 56 patients who completed Part B continued to Part C of the study. The demographic and baseline patient characteristics were representative of the intended patient population. The majority of patients (96.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, with ovary, breast, lung, colorectal, peritoneum, and prostate being the most common primary tumour locations. The patient discontinued due to condition being worsened was excluded from the PK analysis dataset.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Food increased olaparib exposures (based on AUCs), by approximately 8% when compared to fasting conditions (treatment ratio: 1.08; 90% CI: 1.01, 1.16). Although this difference was of borderline statistical significance, since the 90% CI for the AUC treatment ratio fell entirely within 0.8 to 1.25, the study has shown that there is no effect of food on olaparib AUC. However, a high fat meal significantly decreased peak plasma exposures (C_{max}) to olaparib by approximately 21% (treatment ratio: 0.79; 90% CI: 0.72, 0.86) probably resulting from a reduction in the rate of absorption (as also evidenced by the 2.5 hour delay in median t_{max}). It was noted that the delay in t_{max} could be marked in some individual patients (range 1 to 12 hours). Food had no obvious impact on variability in olaparib PK with %GCV for the geometric mean AUC values in the range 55 to 57% independent of the prandial state. Nor

was there any effect of food on the terminal elimination half-life, clearance or volume of distribution.

The results of the study have shown that food (high fat meal) slows the rate (delays t_{max}), decreases peak exposures to drug (C_{max}), and marginally increases the extent of absorption (AUC).

Summary of pharmacodynamic results

Pharmacodynamic (ECG) data is discussed within the safety results section.

Summary of safety results

A total of 86.7% patients in Part A, and 68.3% of patients in Part B experienced at least 1 adverse event (AE), the majority of which were gastrointestinal in origin, and of Common Terminology Criteria for Adverse Event (CTCAE) grade 2 or lower. The number and type of AEs reported during this study were in line with what would be expected for this patient population and the safety profile for olaparib. In Part A, 6 patients reported CTCAE grade 3 AEs, and 1 of these AEs was also a Serious Adverse Event (SAE). In Part B, 1 patient reported 2 CTCAE grade 3 AEs and no SAEs were reported. No AEs leading to discontinuation of olaparib were reported. The AEs reported by the greatest number of patients were nausea (15 [25.0%] patients in Part A, and 18 [30.0%] patients in Part B), vomiting (13 [21.7%] patients in Part A, and 5 [8.3%] patients in Part B), fatigue (7 [11.7%] patients in Part A, and 5 [8.3%] patients in Part B), headache (7 [11.7%] patients in Part A), and diarrhoea (7 [11.7%] patients in Part A, and 4 [6.7%] patients in Part B). There were no clinically relevant differences between the safety profiles of olaparib administered after a high fat meal, compared with the fasted state, and no obvious increase in the incidence of AEs in the SOC gastrointestinal disorders on dosing days, compared with non-dosing washout days. Of the AEs reported during Part A (fed), 8.3% were nausea, and 5.0% were vomiting. During Part B, 18.3% of AEs reported were nausea, with 16.7% vomiting. For all treatment conditions, the most frequent AEs related to olaparib were of gastrointestinal origin. No new safety findings were observed for olaparib (based on the known safety profile for olaparib) during Parts A or B of the study.

Two deaths were reported: 1 during the fed period of Part A and 1 during Part B; both were related to the disease under investigation.

The highest mean increase from baseline in QTcF (SD) in Part A was 0.8 (10.38) ms, and 7.3 (9.84) ms in the fed and fasted periods, respectively, and 4.1 (10.88) ms in Part B. The same patient had absolute QTcF intervals >480 ms in Part A (fasted) and Part B, and no patients experienced QTcF intervals >500 ms. There were 7 (11.7%) patients in Part A and 2 (3.7%) patients in Part B who had increases from pre-dose baseline QTcF >30 ms.

The number of abnormalities in clinical laboratory parameters, vital signs, ECG, and physical examination data was low, with the majority considered to be consistent with the known safety profile of olaparib or the patients' underlying disease.